EXHIBIT I-1

Radiology

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Abbreviations:
DVT = deep venous thrombosis
IVC = inferior vena cava
PE = pulmonary embolism

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Author contribution:
Guarantor of integrity of entire study, M.R.A.

Initial Experience in Humans with a New Retrievable Inferior Vena Cava Filter[1]

PURPOSE: To evaluate preliminary clinical experience in humans with the Recovery nitinol filter (RNF) for the inferior vena cava, especially the efficacy of the device and safety of its retrieval.

MATERIALS AND METHODS: Thirty-two patients were followed up to assess for filter efficacy and for ability to remove the filter.

RESULTS: Sixteen men and 16 women aged 18–83 years (mean, 53 years) underwent treatment with the RNF. Indications for placement were recent pulmonary embolism ($n = 16$), recent deep venous thrombosis ($n = 20$), and/or prophylaxis ($n = 2$). Four patients had contraindications to anticoagulant therapy, and four had complications from anticoagulant therapy. The filter was successfully placed in 32 patients. In 24 (100%) of 24 patients, the filter was successfully retrieved with a jugular approach. The mean implantation period was 53 days (range, 5–134 days). Trapped thrombus was seen within the filter in seven cases. In one patient with a large trapped thrombus, the filter was noted to have migrated 4 cm cephalad. There were no episodes of pulmonary embolism or insertion-site thrombosis.

CONCLUSION: This preliminary experience in humans confirms the efficacy of the RNF. It also demonstrates the feasibility and safety of retrieval up to 134 days after implantation.

Anticoagulation is the accepted standard therapy in patients with venous thromboembolic disease. When contraindications to anticoagulant therapy are present, interruption of the inferior vena cava (IVC) can be performed to prevent the passage of large life-threatening emboli to the lungs. With the introduction of the Greenfield filter in 1973, placement of IVC filters has become accepted as the most common treatment alternative (1). Since the advent of devices that can be placed percutaneously, the number of filters inserted on a yearly basis has increased markedly (2,3). It has been specifically noted that there has been an increase in the implantation rate in young patients (2). Coincidentally, follow-up studies have revealed a 2%–19% incidence of late complications, often arising many years after filter placement (4,5). As the prevalence of patients with IVC filters has increased, so too have reports of guide wire entrapment with subsequent displacement of filters to the heart (6,7). Concerns about the long-term safety of IVC filters have resulted in the suggestion that permanent filters be avoided, especially in patients with a long life expectancy (8).

In many patients, the period of risk from anticoagulant therapy is relatively short. Other than the treatment of patients with widespread malignancy, there are few clinical situations that require placement of a lifelong IVC filter. Several studies have revealed that up to 30% of patients receive anticoagulant therapy following placement of an IVC filter (4,9). Decousus et al (10) demonstrated a reduction in the incidence of pulmonary embolism (PE) in patients with filters compared with patients treated with anticoagulant therapy at the 12-day mark, and no difference in outcome between patients with filters and those treated with standard anticoagulant therapy at 2 years. These researchers also observed an increased risk of recurrent deep venous thrombosis (DVT) in the patients treated with filter placement compared with those treated with anticoagulants alone (10). These data support the use of nonpermanent IVC filters.

There are two varieties of nonpermanent filters—temporary and retrievable. Temporary filters are attached to some form of tether, such as a guide wire or catheter, and thus must be removed (11). The anchoring mechanism of temporary filters often results in some degree of patient immobility and may also serve as a nidus for infection. If filter thrombosis occurs, a new, permanent filter must be placed. Retrievable filters may be left in place permanently or they may be retrieved, depending on what is appropriate for each individual clinical situation. Currently, the only retrievable device approved for use in Canada is the Gunther Tulip filter (Cook Canada, Stouffville, Ontario) (12,13). In their review of data from a multicenter registry, Lorch et al (14) state that filters that can be retrieved or left in place at the option of the physician would be an appropriate kind of temporary filter to use as long as the retrieval procedure was technically easy and had a low complication rate.

Although there are many differences between temporary and retrievable filters, all currently approved devices share a common limitation—length of residence prior to removal. Current instructions for use for most nonpermanent filters state that the filter must be removed within 10–14 days of placement. The predominant concern is the development of endothelialization, which would make subsequent removal impossible. Endothelialization has been shown to lead to explantation problems after as short a period as 12 days (15).

The Recovery nitinol filter (RNF) (NMT Medical, Boston, Mass), a retrievable IVC filter, is a new device (Fig 1). It is composed of 12 0.13-inch nitinol wires that extend from a nitinol sleeve. It has six arms and six legs. The resting diameter of each of the arms is 30.5 mm; the resting diameter of each of the legs is 32 mm. The filter measures 4 cm in height. It has undergone benchtop and animal testing since 1998. On the basis of the evidence that the filter is safe, effective, and retrievable up to 22 weeks after insertion, the purpose of this study was to evaluate our preliminary clinical experience with the efficacy of this filter and the safety of its retrieval in humans.

MATERIALS AND METHODS

Patients and Filter Insertion

Thirty-four consecutive patients who required an IVC filter and who were anticipated to return to anticoagulant therapy 10 days to 12 weeks after the procedure or to not require anticoagulant therapy for 10 days to 12 weeks were selected to receive an RNF between April 2000 and November 2001. Patients were considered for placement of this filter only if their estimated life expectancy was greater than 2 years. Retrieval was planned for all patients. The device was released for use on a special-access basis by the Health Protection Branch of the federal government of Canada, in Ottawa, Ontario, and its use was approved by the University of Toronto ethics department and by the institutional review board. Informed consent was obtained from all patients. Specifically, the option of placement of a permanent filter or an approved removable filter such as the Gunther Tulip retrievable filter (Cook Canada) was offered.

The filters were placed at multiple sites of a multiinstitutional medical imaging department by a single staff vascular and interventional radiologist (M.R.A.). The timing of filter removal was coordinated with the referring physician and/or with special referral to a hematologist. The decision regarding return to anticoagulant therapy was usually made by the referring physician on the basis of his or her assessment of the risk of bleeding versus concern regarding propagation of lower-extremity DVT. All 32 patients who received filters (two patients were found to have anatomic conditions unfavorable for filter placement) had the decision to return to anticoagulant therapy made for them in this fashion. In cases in which it was deemed that filter removal had to be postponed beyond 12 weeks for a medical indication, specific approval from both the ethics department and the Health Protection Branch was sought and granted.

All procedures were performed with standard sterile technique. Conscious sedation was achieved with midazolam (Versed; Sabex, Boucherville, Quebec, Canada) and fentanyl citrate (Sublimaze; Faulding, Dorval, Quebec, Canada), which were simultaneously administered at the patient's request. All devices were placed via the femoral vein on the side contralateral to the side of venous thrombosis, if present. Access was obtained with real-time ultrasonographic (US) control and a 19-gauge single-wall puncture needle (Cook Canada) after local anesthetic with 1% xylocaine (Lidocaine; AstraZeneca, Mississauga, Ontario, Canada) had been applied to the puncture site. A 5-F pigtail catheter (Cook Canada) was subsequently advanced over a 0.035-inch standard J-tip guide wire (Cook Canada), and digital subtraction angiography of the IVC was performed in frontal and lateral projections with hand injection only. The IVC was measured in both planes with a ruler, a dime, or a calibrated catheter and was assessed for duplication and thrombosis. The number and position of the renal veins were also noted. Selective renal vein catheterization was not performed. The filter was not placed if the corrected diameter of the vena cava exceeded 28 mm.

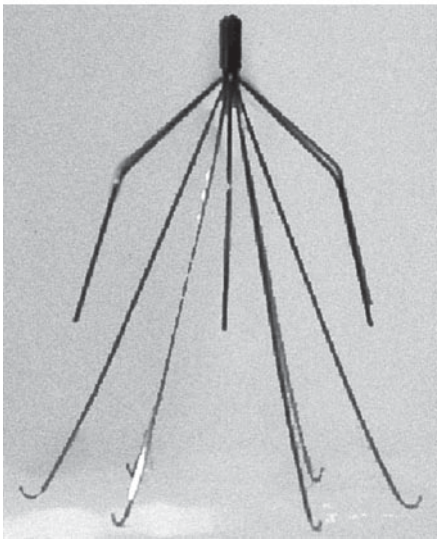


Figure 1. RNF retrievable IVC filter. (Original magnification, ×3.) The device is manufactured from nitinol wire of 0.013 inch in diameter. It is 4 cm in height, and the base can accommodate a vena cava up to 28 mm in diameter. There is dual-level filtration from both the arms and the legs.

In a single instance, the filter was placed by means of a portable C arm in the intensive care unit as a result of concern that this ventilated patient could not tolerate transfer to the interventional suite. In this case, right-sided access was impossible because of the presence of a previously unsuspected iliac venous thrombosis. There was an indwelling left femoral venous line, so a new, separate left femoral puncture was performed. This patient was already undergoing prophylactic broad-spectrum antibiotic therapy for his underlying condition, and he did not subsequently develop signs of sepsis secondary to the procedure.

Following placement of the 6-F introducer sheath, the filter was advanced and deployed with a technique similar to that used with the Simon nitinol filter (NMT Medical). The sheath and filter reservoirs were primed with a standard heparin and saline flush prior to placement. Neither a

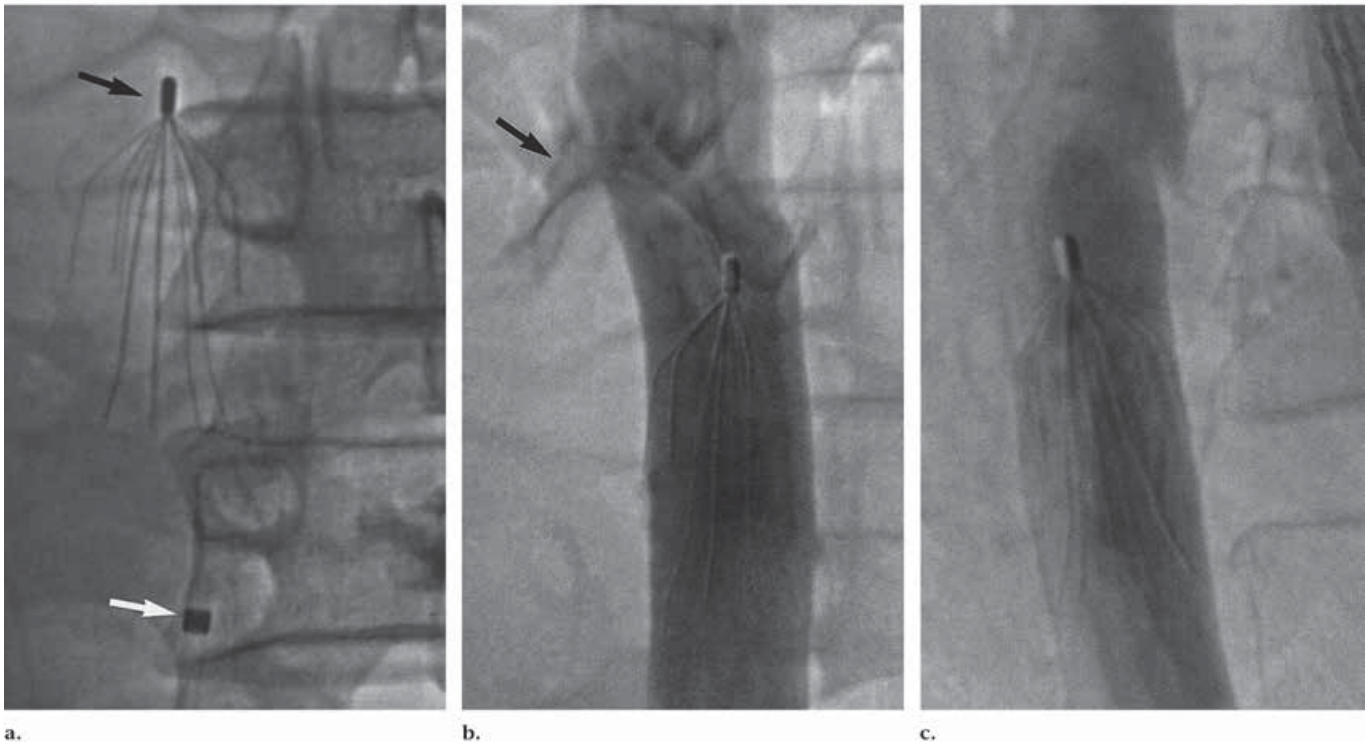


Figure 2. Vena cavograms depict filter placement. **(a)** Frontal scout view obtained just before the postinsertion vena cavogram shows the highly visible nitinol RNF filter with its tip at the L1-2 interspace (black arrow). Note the radiopaque marker band on the tip of the insertion sheath (white arrow). **(b)** Frontal postinsertion vena cavogram demonstrates that the filter is aligned with the caval axis, with its tip approximately 1 cm caudal to the right renal vein (arrow). **(c)** Lateral vena cavogram demonstrates alignment in this plane as well.

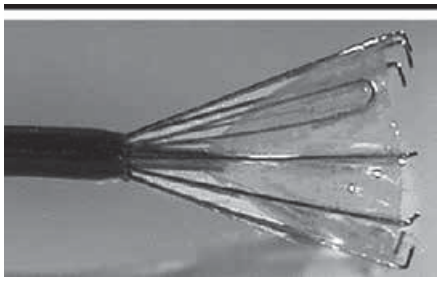


Figure 3. Retrieval cone, which is constructed with nine metal claws covered by a urethane cover. The open diameter of the cone is 15 mm. A central lumen allows for over-the-wire placement. The cone is inserted via the jugular vein through a 10-F profile catheter with a radiopaque band on its end.

drip infusion nor iced saline was used. The filter was released by maintaining the position of the pusher while retracting the sheath at the target site. This filter does not shorten when it opens; this allows for accurate deployment at the target. Follow-up digital subtraction angiography of the IVC was performed in both frontal and lateral projections to assess for filter alignment with the caval axis and to confirm the position of the filter with respect to the renal veins (Fig 2). The sheath was then removed, and hemostasis was achieved. Subsequent anticoagulant therapy was commenced at the discretion of the referring physician.

Filter Removal

Filter removal was performed when it was deemed that the patient could safely resume full and uninterrupted anticoagulant therapy. In some patients, a trial of anticoagulation was performed before planned filter removal to avoid the need for filter reinsertion. Any anticoagulant therapy was subsequently reversed at the time of removal. Therapy with warfarin sodium (Coumadin; DuPont Pharma, Mississauga, Ontario, Canada) was maintained before scheduled filter removal until the international normalized ratio was less than 1.3. In patients receiving dalteparin sodium (Fragmin; Pharmacia, Mississauga, Ontario, Canada), the scheduled dose prior to filter removal was withheld.

Removals were performed with standard aseptic technique and conscious sedation protocols similar to those used in filter insertion. All procedures were performed via the right jugular vein with real-time US control. Initially, a 5-F pigtail or multipurpose catheter, advanced over a guide wire, was placed in a location below the filter so that digital subtraction angiography of the vena cava could be performed in both frontal and lateral projections. The angiograms were assessed for filter position and tilt with respect to the caval axis and to identify trapped thrombus. Following insertion of a 0.035-inch Amplatz extrastiff straight guide wire (Boston Scientific, Mississauga, Ontario, Canada), the 10-F retrieval sheath was placed. It was occasionally necessary to predilate the tract with a 10-F Coons dilator (Cook Canada). The retrieval cone (Fig 3) was then advanced through the sheath and docked with the filter tip so that the filter could be retracted into the sheath and removed.

It was sometimes necessary to advance a 0.035-inch angled guide wire (Terumo; Sultzer Medical, Mississauga, Ontario, Canada) or a 5-F multipurpose catheter (Cook Canada) to facilitate the docking procedure. The guide wire could be advanced through the central lumen of the retrieval cone, whereas the 5-F multipurpose catheter could be introduced through

the retrieval sheath. With increased experience, the procedure was changed so that the initial catheter was selectively placed toward the side of the filter at which the shortest distance between the filter tip and the caval wall was seen at the time of initial angiography. The retrieval sheath was subsequently advanced over a 260-cm-long Amplatz wire. With this technique, any subsequent additional manipulations to dock the cone and filter became unnecessary.

Following removal, a repeat vena cavogram was obtained to assess for procedural trauma or any other complication related to filter residence. The filters were examined for trapped thrombus, endothelium formation, and mechanical damage. The sheath was then removed and hemostasis was achieved. Anticoagulant therapy was restarted under the direction of the referring physician or attending hematologist. The filters were returned to the manufacturer (NMT Medical) so that a complete assessment of device integrity could be performed.

Follow-up

Abdominal radiography 1 and 7 days after placement, then yearly, was recommended per our protocol for follow-up after placement of permanent IVC filters. No other routine follow-up imaging studies were performed because this device was placed on a compassionate basis, not under the confines of a scientific study protocol. However, in any patient in whom an adverse event was clinically suspected, appropriate imaging studies were performed (Fig 4). In patient 10 and all subsequent patients, routine follow-up abdominal radiographs were obtained to assess for possible filter migration. This change in protocol was instituted after identification of an episode of asymptomatic migration of the filter in patient 9. It was specifically requested that these radiographs be sent directly to the author to enable direct comparison of the position of the filter on subsequent radiographs with its position on radiographs obtained at the time of placement.

Several of the patients in this series underwent repeat radiologic examinations after filter removal as part of their routine medical care. When available, images from these examinations were evaluated to identify any postinsertion or removal complications. Clinical follow-up of patients after filter removal was achieved by means of the author's review of subsequent, forwarded medical notes or by direct telephone contact with the patient. On all images, filters were evaluated for tilt, migration, trapped thrombus, and caval perforation. During follow-up visits, patients were evaluated for signs or symptoms of insertion-site or vena caval thrombosis and PE. All radiologic images were evaluated by the author, and all clinical examinations were performed by the referring physician.

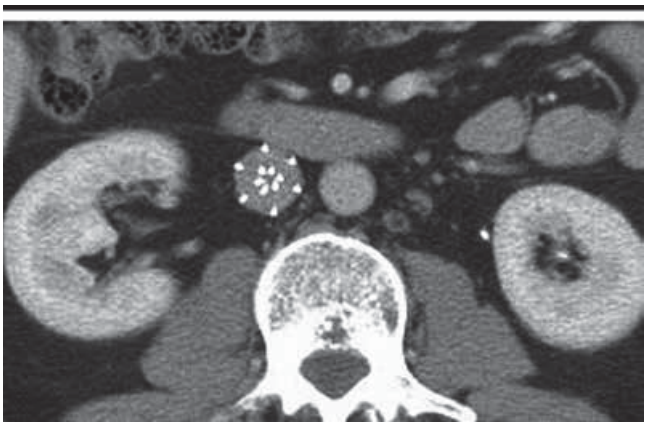


Figure 4. Follow-up transverse contrast material–enhanced spiral computed tomographic (CT) scan obtained as part of this patient's routine medical care 2 weeks after placement of an RNF shows the filter to be in good position, with no associated complication.

RESULTS

Placement of a temporary filter was requested in a total of 34 patients. In one patient, the corrected caval diameter measured 33 mm on the vena cavogram. The referring physician did not want placement of a permanent filter, so no filter was placed in that individual. In one patient with DVT who was scheduled for orthopedic surgery, there was congenital interruption of the vena cava with hemiazygous continuation, so no filter was placed. In all other instances, patients consented and received the RNF (Table 1). Mean patient age was 53 years (range, 18–83 years). There were 16 male and 16 female patients. A diagnosis of DVT was confirmed with color Doppler US in 23 patients; 18 patients had right-sided DVT, and five patients had left-sided DVT. A diagnosis of PE was confirmed in 15 patients at CT angiography.

In four of 26 patients in whom anticoagulant therapy was contraindicated, it was contraindicated because of an underlying coagulopathy. In two patients anticoagulant therapy was contraindicated because the patient had recently undergone surgery, and in 18 patients it was contraindicated because the patient was scheduled to undergo surgery. Four patients had experienced a complication during anticoagulant therapy. In two patients at high risk for PE, filters were placed prophylactically. One filter was placed in a patient with pulmonary hypertension and multiple pulmonary emboli. Filters were placed in two patients in whom pulmonary CT angiograms were initially interpreted as positive for PE by the on-call body imaging staff but in whom final dictated radiology department reports indicated no PE. One of these patients had a remote history of DVT, so the filter was temporarily left in place. In the other patient there was no evidence of DVT, so the filter was removed at 5 days.

Sixteen patients had been given an underlying diagnosis of malignant neoplasm. Patients were referred from the departments of orthopedic surgery (n = 9), surgical oncology (n = 6), general surgery (n = 3), respirology (n = 3), intensive care (n = 2), internal medicine (n = 4), nephrology (n = 2), cardiology (n = 1), neurosurgery (n = 1), and medical oncology (n = 1) (Table 2). Fifteen patients (47%) received concomitant anticoagulant therapy for some period of time while the filter was in place.

Filter Insertion

In one instance, the filter could not be advanced through the introducer sheath. It was unclear whether the problem was that the filter had been loaded incorrectly into the sheath at the time of packaging or if there was inadvertent disengagement of the pusher at the time of insertion. In that patient, the sheath was removed, a new puncture was made, and

TABLE 1
Patient Data

Patient No./Age (y)/Sex	Underlying Diagnosis	Proven DVT	Proven PE	Indication for Filter Placement	Filter Retrieved, Duration of Filter Presence (d)	Confirmed Trapped Thrombus	Patient Outcome
1/55/M	Colon cancer	Yes	Yes	Placed after resection for possible repeat surgery for small bowel obstruction	Yes, 10	Yes	No disease progression
2/35/F	Leukemia	Yes	No	Thrombocytopenia, respiratory failure	No, 41	No	Deceased
3/78/F	Colon cancer	Yes	Yes	Placed before bowel resection	Yes, 29	No	No disease progression
4/22/F	Pyonephrosis	No	Yes	Bilateral nephrostomy, then lithotripsy	Yes, 50	No	Resolution of disease
5/28/M	Crohn disease, giant cell sarcoma	Yes	No	Gastrointestinal bleeding (spontaneous)	Yes, 75	No	Stable
6/30/M	Mesenchymal sarcoma	Yes	Yes	Placed before resection of primary pelvic tumor	No, 59	No	Deceased
7/84/M	Hip fracture, stroke, bladder outlet obstruction	Yes	No	Femoral pseudoaneurysm secondary to carotid stent placement	Yes, 83	No	Ongoing bladder problems (prostatic hypertrophy)
8/58/F	Polyarteritis, pulmonary aspergillosis	Yes	No	Gastrointestinal bleeding secondary to gastric erosions	No, 15	No	Deceased
9/61/M	Coronary artery disease, myocardial infarction	Yes	Yes	Puncture-site complication following emergency coronary artery stent placement (large retroperitoneal hematoma); filter placed before surgical repair and vascular grafting	Yes, 17	Yes	Stable
10/29/F	Chronic renal failure, renal transplant, acute thrombocytopenia secondary to *Escherichia coli* infection	Yes	No	Intraabdominal bleeding after hemicolectomy, thrombocytopenia, and acute renal failure (of transplant)	Yes, 34	Yes	Complete recovery of renal function, reversal of iliostomy
11/70/M	Chrondrosarcoma	Yes	No	Placed before resection of primary tumor	Yes, 65	No	Tumor free
12/37/F	Postpartum hemorrhage, multisystem failure	Yes	No	Cardiac arrest, liver and renal failure, fourth-degree vaginal tear with bleeding	Yes, 21	No	Recovered
13/32/F	Osteosarcoma	Yes	No	Placed before resection of primary tumor	Yes, 71	No	Tumor free
14/67/F	Pelvic sarcoma	Yes	No	Placed before resection of primary tumor with vascular reconstruction	Yes, 55	No	Developed metastatic disease
15/71/F	Lymphoma	No	Yes*	Chemotherapy, thrombocytopenia	Yes, 5	No	Remains in hospital with multiple medical problems†
16/50/M	Chronic renal failure but no dialysis	Remote history of DVT	Yes*	Development of buttock hematoma during warfarin therapy (international normalized ratio, 2.3)	Yes, 70	No	Resolution of disease
17/33/M	Crohn disease	Yes	No	Intraabdominal abscess; filter placed before percutaneous drainage and bowel resection	Yes, 40	No	Resolution of disease
18/46/F	Retroperitoneal sarcoma	Yes	No	Placed before surgical resection of primary tumor	Yes (surgically), 11	No	Stable
19/44/M	Lung cancer	No	Yes	Placed before surgical resection of primary tumor	Yes, 61	No	Tumor free
20/77/F	Colon cancer	No	Yes	Gastrointestinal bleeding during warfarin therapy; filter placed before surgical resection of primary tumor	Yes, 49	Yes	Stable
21/70/F	Colon cancer	No	Yes	PE 3 mo before planned liver resection	Yes, 21	Yes	Stable
22/65/M	Pelvic chondrosarcoma	Questionable‡	No	Placed before surgical resection (patient thought to be at high risk for postoperative DVT given planned vascular reconstruction)	Yes, 14	No	Tumor free
23/49/M	Pulmonary hypertension	Yes	Yes	Newly diagnosed pulmonary hypertension thought to be because of recurrent PE, poor pulmonary reserve	Yes, 77	No	Stable; being considered for embolectomy†
24/47/F	Squamous cell carcinoma of anus	Questionable‡	No	Placed before surgical biopsy of pelvic nodal mass	Yes, 134	No	Slowly progressive metastatic disease
25/74/F	Periprosthetic fracture	Yes	No	Placed before surgical revision	Yes, 91	Yes	Recuperating†
26/80/M	Total knee replacement	Yes	No	Postoperative bleeding at surgical site	Yes, 103	No	Ongoing bleeding; anticoagulant therapy stopped†
27/82/F	Periprosthetic hip fracture	No	Yes	Placed before surgical revision	Yes, 91	No	ND§
28/61/M	Osteoarthritis	Yes	No	Placed before total hip replacement	Yes, 83	No	ND§
29/50/M	Leg osteosarcoma	No	Yes	Chemotherapy followed by surgical resection	NA‖	NA‖	NA‖
30/18/F	Cerebral palsy	No	Yes	Upper gastrointestinal bleeding secondary to severe esophageal ulceration	NA‖	NA‖	NA‖
31/71/F	Hemorrhagic stroke	Yes	Yes	Hemorrhagic stroke	NA‖	NA‖	NA‖
32/35/M	Subdural hematoma	No	Yes	Recent neurosurgery	NA‖	NA‖	NA‖

* On false-positive CT scan.
† At time of writing.
‡ At magnetic resonance (MR) imaging.
§ ND = no data.
‖ NA = not applicable (filter in place at time of writing).

a filter was placed without further difficulty. In another case, the filter was incompletely advanced out of the sheath, causing the leg hooks to engage the sheath. It was possible to recapture the filter tip with the stabilizer arm and then push the filter out of the sheath. This filter did remain in an infrarenal position. All other filters were placed in an infrarenal position without incident. Twenty filters were placed via the left femoral vein, and 12 were placed via the right.

In the placement of 17 (74%) of the first 23 filters, there was some difficulty in releasing the filter legs from the splines of the stabilizer arm. This was overcome by moving the introducer sheath in a gentle twisting motion. This problem had not been encountered in animal testing. Investigation by employees of NMT Medical revealed that the polishing process during manufacturing resulted in a "rolling over" of the edges of the splines, which caused the filter legs to tend to catch when the device was angulated at the time of attempted release. After the tumbling process was changed, the release problem did not recur.

Tilt of the filter with respect to the caval axis (defined as tilt > 15°) was encountered in two (6%) of 32 deployments. The tilt was 20° and toward the side contralateral to the venous puncture in both cases. Each instance of tilt occurred in the first 23 placements, with associated difficulty in release from the splines.

Complications and Filter Removal

No patient developed a substantial puncture-site hematoma or any other complication related to filter insertion or removal. No patient developed symptomatic PE or insertion-site DVT following filter placement or removal (Table 3). One patient with a preoperatively placed filter experienced left-sided hemiplegia 10 hours after surgical revision of a fractured hip prosthesis. Her symptoms completely resolved, and a thorough neurologic evaluation revealed that she had had a transient ischemic attack unrelated to the filter. The filter in this patient was found to contain a small thrombus at the time of an abdominal CT examination.

Thrombus trapped within the filter was encountered in five additional patients at the time of filter removal, for a total of seven (22%) of 32 patients. In three patients the thrombus burden was small, and the filters were removed with a standard technique and the standard retrieval sheath (Fig 5). Two filters were found to contain a large thrombus at the time of elective removal. In one patient, the filter was also noted to have migrated approximately 4 cm cephalad at the time of planned elective removal 17 days after insertion (Fig 6a, 6b). In retrospect, a lesser degree of migration was noted on a follow-up abdominal radiograph that had been obtained 4 days earlier; however, the migration had not been indicated in the typed radiology report.

After extensive discussion with the patient and referring physicians, it was decided that filter removal should be attempted. In this case, a 20-F vascular sheath (Cook Canada) was inserted and the RNF sheath was placed through it. The filter and thrombus were removed together (Fig 6c–6e). Although the patient was asymptomatic, CT angiography of the pulmonary arteries and CT venography of the IVC were performed to assess for local residual thrombus or PE. No evidence of either was seen. Two other patients underwent CT angiography of the pulmonary arteries at the time of filter removal (one filter had a trapped clot, and one did not); there was no evidence of PE in either of these patients.

Three patients died of their underlying disease with the filter in place 15 to 59 days (average, 38 days) after placement without clinical evidence of PE. Autopsy information was not available for any of these patients. One filter was removed intraoperatively as a result of a surgical mishap during attempted resection of a large retroperitoneal sarcoma. Twenty-four filters were removed 5–134 days (mean, 53 days) after insertion; as of this writing, four remain in place for planned removal. All attempted filter removals were successful (Fig 7). Once the sheath was in place, filter retrieval always took less than 2 minutes. Several patients noted momentary mild epigastric or back pain at the time the filter was removed. Otherwise, the majority felt only some manipulation of the jugular venous sheath.

Follow-up

Many patients continue to undergo medical and radiologic follow-up as a result of their underlying disease process (Table 4). Records from medical visits and/or abdominal CT examinations were available in 22 (92%) of the 24 patients who had undergone filter removal. The average length of follow-up was 223 days (range, 4–522 days). Follow-up data included information obtained from abdominal CT examinations in seven patients, chest CT examinations in four patients, and clinical care visits or telephone interviews in 20 patients. One patient developed clinical symptoms suggestive of PE 133 days after filter removal. However, repeat CT angiography of the lungs did not depict PE.

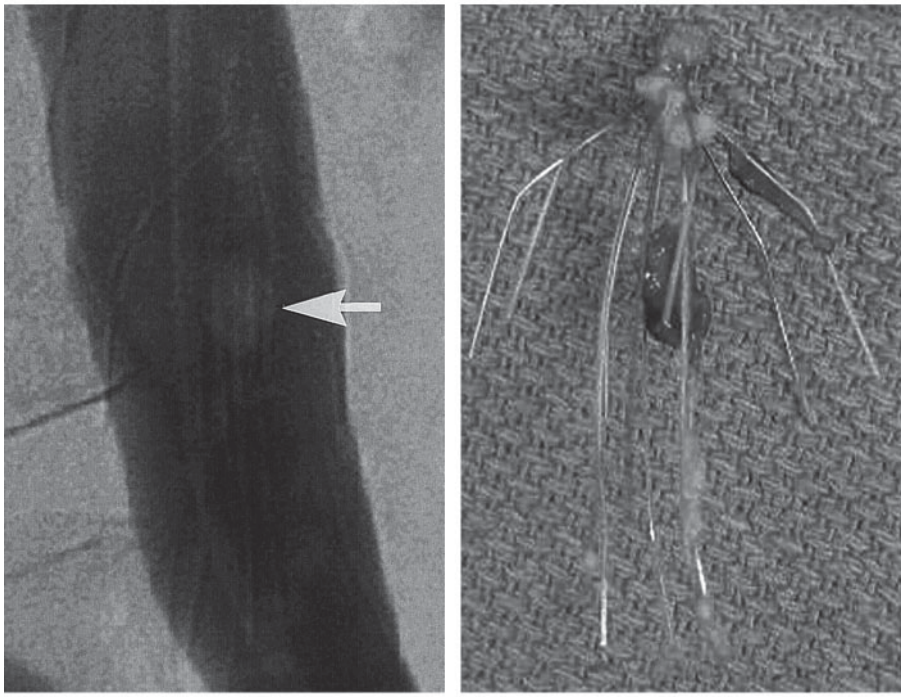
As of this writing, no other patient has developed clinical symptoms or imaging findings suggestive of PE, recurrent DVT, or any caval abnormality. One patient experienced recurrent hemorrhage at the surgical site (of a total knee replacement) 8 days after the filter was removed and therapy with dalteparin sodium had been reinstituted. This patient had previously tolerated a 2-week course of dalteparin sodium before filter removal. The indication for filter placement in this patient was PE without documented DVT. Because it had been 100 days since PE occurred, the attending hematologist believed it was safe to discontinue anticoagulant therapy.

TABLE 2
Patient Demographics

Characteristic	No. of Patients
Diagnosis	
DVT	23
PE	15
Reason for filter placement	
Anticoagulant therapy contraindicated	26
Anticoagulant therapy had resulted in complications	4
Coagulopathy	4
Prophylaxis	2
Poor pulmonary reserve	1
Subsequent surgery	18
Referring department	
Orthopedic surgery	9
Surgical oncology	6
Internal medicine	4
General surgery	3
Respirology	3
Intensive care	2
Nephrology	2
Neurosurgery	1
Medical oncology	1
Cardiology	1

TABLE 3
Number of Patients with Complications

Complication	No. of Patients
Failure (PE with filter in place)	0
Insertion site thrombosis	0
IVC thrombosis	0
Filter migration (>2 cm)	1
Filter tilt (>15°)	2



a. b.

Figure 5. Thrombus removal. **(a)** Vena cavogram obtained with a 5-F multipurpose catheter inserted via the right internal jugular vein at the time of filter removal (10 days after placement) reveals a small trapped embolus within the filter (arrow). **(b)** Gross specimen obtained after removal of filter and embolus with a standard 10-F sheath. Note embolus trapped by filter legs.

TABLE 4
Patient Follow-up

Outcome	No. of Patients
Intraoperative filter removal	1
Death	3
Percutaneous filter removal	24
Follow-up visit, follow-up radiology	22*
Clinic visit	20
CT of abdomen	7
CT of thorax	4

Note.—Thirty-two filters were placed in 32 patients.

* Follow-up records were available in only 22 of the 24 patients who underwent percutaneous filter removal.

DISCUSSION

The RNF IVC filter is manufactured by NMT Medical. Constructed of nitinol, this filter is modeled after the dual-level structure of the Simon nitinol filter, which NMT Medical also manufactures. Several designs of a temporary retrievable filter were investigated before the current design for the RNF was conceived in 1998. One of the key features of the RNF that allows for retrieval many months after implantation is the hook design. The hooks of this filter were specifically designed, modeled, and tested to resist filter migration. The RNF underwent extensive benchtop and animal evaluation before it was first placed in a human patient (16).

Interest in a retrievable IVC filter has intensified since the first reported successful retrieval of an Amplatz filter (William Cook Europe, Bjaeverskov, Denmark) by Darcey et al in 1986 (17). However, this device was withdrawn from sale as a result of a high rate of vena caval thrombosis (18). There are currently a variety of tethered removable filters available in North America; however, they are not commonly placed as a result of their intrinsic design limitations.

The medical need for a retrievable filter design is demonstrated by the off-label use of currently approved permanent filters. Cope et al (19) described partial deployment of a Bird's Nest filter (Cook, Bloomington, Ind) during thrombolysis of iliocaval thrombus. The filter was safely removed 6.5 hours later (19). More recently, Nutting and Coldwell (20) completely deployed a TrapEase filter (Cordis, Miami, Fla), also for temporary protection during thrombolysis. Nutting and Coldwell described using a combined jugular and femoral venous approach to retrieve the filter after the procedure (20).

Although these maneuvers have proven to be successful in these case reports, they clearly contravene the manufacturer's instructions for use and place the patient at risk for a complication or failure of removal. A more common indication for filter removal is filter migration, either occurring at the time of implantation or seen at follow-up (21–23). Perhaps less common as an indication for removal is filter infection. Millward et al (24) reported a death attributed to an infected filter (Vena Tech; B Braun, Mississauga, Ontario, Canada). More recently, Lin et al (25) reported the successful removal of an infected Gunther Tulip filter 14 days after implantation. Another indication well suited for a retrievable IVC filter is that of trauma (26,27).

The Gunther Tulip filter was approved for both permanent placement and retrieval in Canada in March 1998. In the United States, it is approved for permanent use. Although the instructions for use state that the filter should be removed by 10 days, Millward et al (28) have reported removal up to 25 days after implantation. However, in an earlier animal study, one of 21 Gunther Tulip filters could not be retrieved 14 days after insertion as a result of adherence to the caval wall (29). Recently published data from the registry of the Canadian Interventional Radiology Association regarding the placement of 91 Gunther Tulip filters currently represent the most extensive experience with that device (28). In that series, one filter could not be retrieved because the hook could not be engaged by the snare. Fifty-two filters were successfully removed at a mean of 9 days after placement. Of the 37 patients who were followed up, four required reinsertion of a permanent filter at a mean of 78 days after removal. Filters were not removed from 17 patients as a result of ongoing contraindications to anticoagulant therapy (28). These results support the need for a filter that can be removed well beyond a 10–15-day window.

The perfect temporary IVC filter would be one that has high clot-trapping efficacy but a low incidence of caval thrombosis. It would have to be nonmigratory yet be able to be retrieved at a time distant from the time of insertion. Finally, there should be no external tether to limit patient mobility or serve as a nidus for infection. While intimal hyperplasia is expected to occur with any implanted device, there are filter design factors that

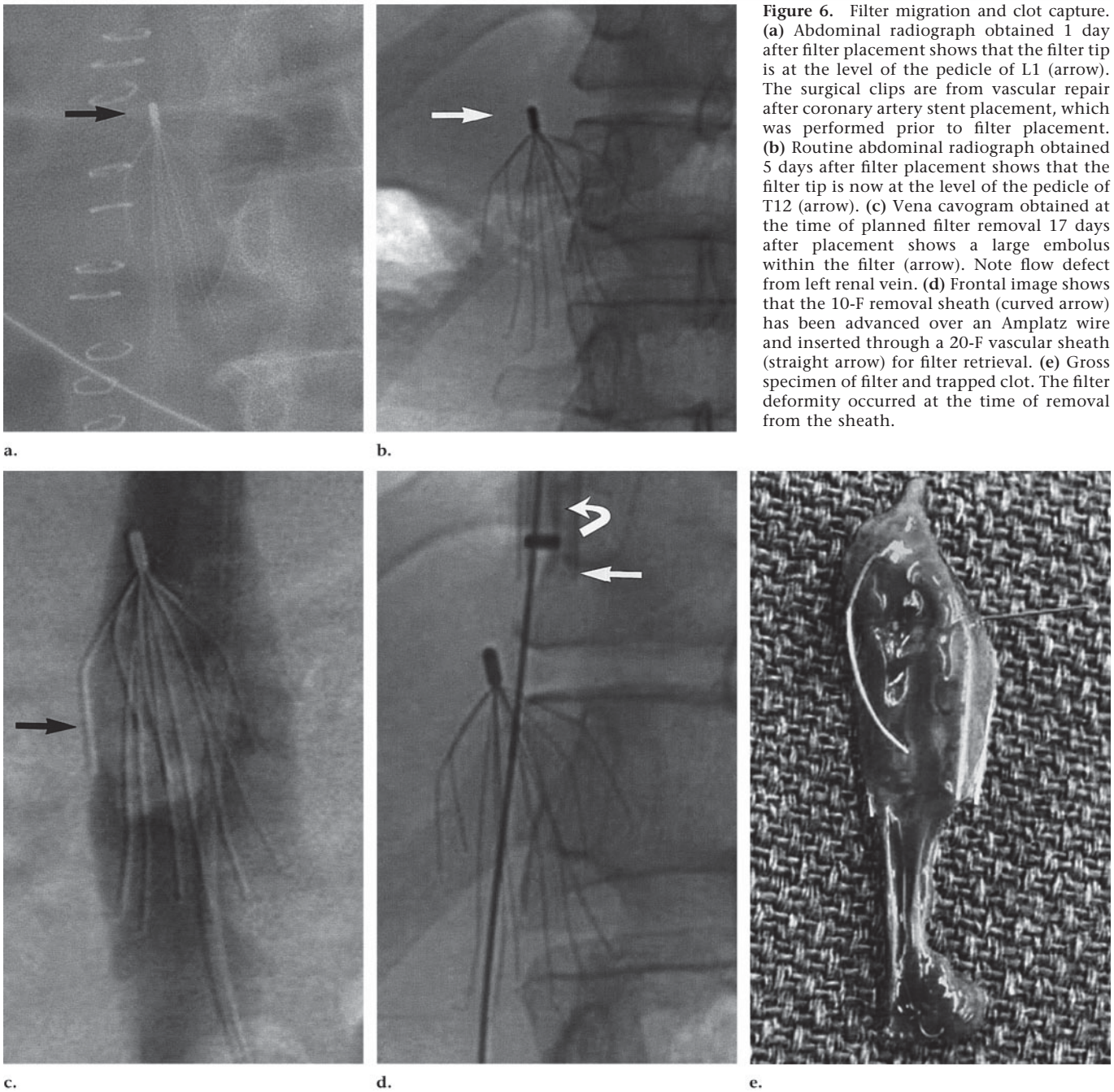
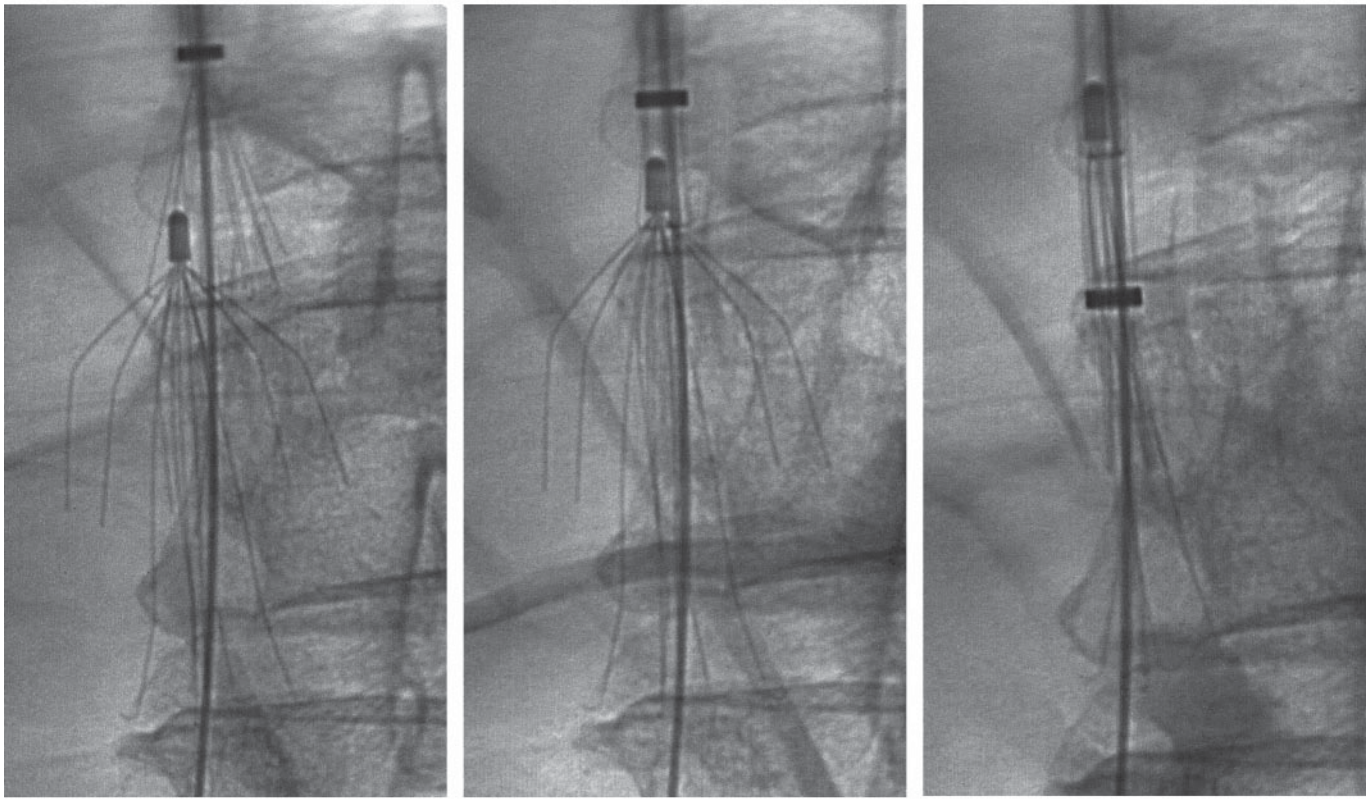


Figure 6. Filter migration and clot capture. **(a)** Abdominal radiograph obtained 1 day after filter placement shows that the filter tip is at the level of the pedicle of L1 (arrow). The surgical clips are from vascular repair after coronary artery stent placement, which was performed prior to filter placement. **(b)** Routine abdominal radiograph obtained 5 days after filter placement shows that the filter tip is now at the level of the pedicle of T12 (arrow). **(c)** Vena cavogram obtained at the time of planned filter removal 17 days after placement shows a large embolus within the filter (arrow). Note flow defect from left renal vein. **(d)** Frontal image shows that the 10-F removal sheath (curved arrow) has been advanced over an Amplatz wire and inserted through a 20-F vascular sheath (straight arrow) for filter retrieval. **(e)** Gross specimen of filter and trapped clot. The filter deformity occurred at the time of removal from the sheath.

would limit the associated adverse effects. It is the author's hypothesis that the ability to retrieve a filter without concern for the amount of hyperplasia requires a filter to have little metal in contact with the caval wall.

Filter design is also important. If one looks at the design of the Gunther Tulip filter or the TrapEase filter, it becomes evident that the complex metal matrix would serve to anchor the filter in place when hyperplasia occurs. On the other hand, the design of the RNF allows for the filter arms to slide out of any potential sleeve once the elastic leg hooks have been removed from the caval wall. The animal data demonstrating the ability to remove an RNF at 22 weeks, coupled with the fact that one was removed from a human at 134 days, suggest that there is no upper limit to the time of retrieval with the current design. In contrast, studies of virtually all other filter designs included cases in which the filter could not be removed 2 weeks after insertion (15,29). Given that intimal hyperplasia stabilizes at approximately 3–6 weeks, one would expect that beyond that time filter fixation is not an issue.

The simple fact that a retrievable device is available is of limited clinical importance if that device must be removed by 10–15 days after placement. In the ideal situation, a patient could safely undergo anticoagulant therapy after surgery. However, even from this relatively small series, it is clear that many patients have more complex situations and require a much longer period of time before they can be



a. b. c.

Figure 7. Sequence of vena cavograms illustrates the technique of removing a filter with a wire. **(a)** The retrieval cone is advanced over a wire, **(b)** the filter arms are engaged, and **(c)** the filter is retrieved.

maintained on uninterrupted therapeutic doses of anticoagulants. Several of the patients referred from orthopedics who underwent routine surgery to install a joint prosthesis had not resumed full ambulation even at 90 days after filter placement. Patients referred from general surgery often require follow-up procedures (such as percutaneous abscess drainage or a second surgical procedure) after surgery.

Although the most common device used for percutaneous removal of foreign bodies is some type of snare, techniques used with this device are not always successful. In the series of Millward et al (28), there was one failed retrieval as a result of the position of a Gunther Tulip filter hook with respect to the caval wall. In spite of moderate angulation in several cases in this series, all filters were easily and successfully retrieved. The urethane-covered claws modeled into a cone shape enabled the efficient engagement and retrieval of the RNF. The ability to pass a 0.035-inch wire through the central lumen of the cone greatly facilitated the docking procedure when there was no straight-line access to the filter tip. As our experience grew, changes in technique occurred. During the final four retrievals, the catheter was intentionally manipulated toward the side of filter tilt and the cone was always advanced over a wire. In this way, no additional maneuvers were required to engage the filter and cone.

There was a single occurrence (3%) of asymptomatic filter migration in this series of 32 patients. Migration is typically defined in the literature as movement greater than 2 cm. The reported incidence has been shown to vary between less than 1% and 13% and typically includes spontaneous migration to the heart (4,24,30,31). In our study patient, the filter was seen to be in a position several centimeters cranial to the insertion position on the radiograph obtained 5 days after insertion. However, the typed radiology report simply stated "An IVC filter is in place." At the time of planned removal at 17 days, the filter was seen to have migrated an additional 2 cm craniad. The vena cavogram obtained before removal revealed a large trapped embolus. It was possible to remove this filter and trapped embolus with the standard retrieval cone introduced through a 20-F sheath. That event was reported to the Health Protection Branch and to our institutional review board, and the consent form was subsequently modified to include information on it.

As a precaution, all subsequent patients underwent follow-up abdominal radiography to assess for filter migration. This fact was emphasized to both the referring physician and the patient. It was requested that all radiographs be sent directly to the author so that he did not have to rely on the dictated report. No other instance of filter migration was encountered. In one patient, several filter arms were seen to lie outside of the vena cava (at venography and CT). However, this patient was asymptomatic, and the filter was easily removed (at 134 days). This patient had undergone an abdominal surgical procedure 2 days after filter placement. Filter penetration of the caval wall has been reported to occur with an incidence of 9% (4).

Although in the present study, filters were placed on a compassionate basis—outside a formal scientific trial—patients were followed up prospectively. Given that this study represents the initial human use of a new medical device, pa-

tients were also promptly and thoroughly examined for any questionable complication. A number of patients underwent CT examination of the abdomen after filter placement and removal to assess for local complications; none was encountered.

In this series of 32 patients, filter efficacy was demonstrated by the fact that there were no episodes of PE and that trapped embolus was seen within the filter in seven cases. Complications such as caval occlusion or insertion-site thrombosis did not occur. The filter was successfully removed in all patients, even when a large trapped thrombus was present. The average time to filter removal in our experience (53 days) is well beyond the residence period for other removable/retrievable filters. The complexity of the clinical situation in these patients is shown by the need to maintain the filter in place for more than 100 days in two of our patients. The ability to remove this filter after such lengthy residence will likely prove to be important and will allow the majority of patients to receive a temporary filter instead of the permanent device used as part of the current standard of treatment. A large multicenter scientific study is warranted to further substantiate the role and value of this retrievable filter.

In conclusion, this preliminary, special-access use of the RNF, a retrievable IVC filter, suggests that the filter can easily be delivered via a femoral vein. It can be removed percutaneously up to 134 days after insertion without difficulty. No substantial complications were encountered in this series. Specifically, there were no documented incidents of PE, caval thrombosis, or insertion-site DVT with the filters in place. Retrieval via the jugular vein allows for removal of filters with small-to-large trapped thrombi.

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